What is claimed is:

1. A method for determining whether a first test protein is capable of interacting with a second test protein, said method comprising:

(a) providing a first population of mating competent cells, wherein a plurality of the cells of said population contain:

(*i*) a first counterselectable reporter gene operably linked to a first DNA-binding-protein recognition site; and

(*ii*) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising said first test protein covalently bonded to a DNA-binding moiety which is capable of specifically binding to said DNA-binding-protein recognition site;

(b) providing a second population of mating competent cells, wherein a plurality of the cells of said second population contain:

(*i*) a second counterselectable reporter gene operably linked to a second DNA-binding-protein recognition site; and

(*ii*) a second fusion gene which expresses a second hybrid protein, said second hybrid protein comprising said second test protein covalently bonded to a gene activating moiety;

(c) maintaining said first and said second populations of mating competent cells, independently, under conditions such that expression of said selectable/counterselectable reporter genes inhibits the growth of said cells;

(d) mixing said first and said second populations of mating competent cells under conditions conducive to formation of mated cells; and

(e) detecting expression of a reporter gene as a measure of the ability of said first test protein to interact with said second test protein, wherein said reporter gene is said first or said second reporter gene or another reporter gene included in said first or said second mating competent cells or said mated cells, and is operably linked to either said first or second DNA-binding-protein recognition sites.

2. The method of claim 1, wherein said first test protein comprises a randomly generated peptide sequence.

3. The method of claim 1, wherein said second test protein comprises a randomly generated peptide sequence.

4. The method of claim 1, wherein said first test protein comprises an intentionally designed sequence.

5. The method of claim 1, wherein said second test protein comprises an intentionally designed sequence.

6. The method of claim 1, wherein said populations of cells are yeast cells.

7. The method of claim 6, wherein said yeast is *S. cerevisiae*.

8. The method of claim 7, wherein one said population of cells is of the MATa mating type and the other said population of cells is of the MATα mating type.

9. The method of claim 1, wherein said first and second counterselectable reporter genes are selected from the group consisting of *URA3*, *LYS2*, and *GAL1*.

10. The method of claim 1, wherein said DNA-binding moiety comprises the DNA-binding domain of a protein selected from the group consisting of GAL4, LexA, and Ace1.

11. The method of claim 1, wherein said gene activating moiety comprises the transcription activation domain of a protein selected from the group consisting of GAL4, VP16, and Ace1.

12. The method of claim 1, wherein said first and second DNA-binding-protein recognition sites comprise at least one binding site for a protein selected from the group consisting of GAL4, LexA, and Ace1.

13. The method of claim 1, wherein the number of each of said first and second DNA-binding-protein recognition sites is between 1 and 20.

14. The method of claim 1, wherein said counterselectable gene is integrated into the genome of said mating competent or mated cells.

15. The method of claim 1, wherein said counterselectable reporter gene is operably linked to a promoter which carries an upstream repressing sequence.

16. The method of claim 15, wherein said counterselectable reporter gene is operably linked to a *SPO13* promoter.

17. The method of claim 1, wherein said expression of said counterselectable reporter gene is detected as inhibition of cell growth.

18. A method for determining whether a test compound is capable of disrupting binding between a first test protein and a second test protein, said method comprising:

(a) providing a cell containing:

(i) a counterselectable reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a first fusion gene expressing a first hybrid protein comprising said first test protein covalently bonded to a DNA-binding moiety which is capable of specifically binding to said DNA-binding-protein recognition site; and

(iii) a second fusion gene expressing a second hybrid protein comprising said second test protein covalently bonded to a gene activating moiety, wherein said second test protein binds said first test protein in the absence of said test compound;

(b) contacting said cell with said test compound under conditions such that expression of said counterselectable reporter gene inhibits cell growth; and

(c) detecting inhibition of expression of said counterselectable reporter gene as a measure of the ability of said compound to disrupt said binding between said first and said second test proteins.

19. The method of claim 18, wherein expression of said reporter gene is detected by detecting growth of said cell.

20. The method of claim 18, wherein said test compound is a protein.

21. The method of claim 20, wherein said protein which is encoded by a nucleic acid contained within a nucleic acid library.

22. The method of claim 20, wherein said protein comprises a randomly generated peptide sequence.

23. The method of claim 18, wherein said first test protein is cJun and said second test protein is selected from the group consisting of cFos and cJun.

24. The method of claim 18, wherein said first test protein is E2F1 and said second test protein is pRB.

25. The method of claim 18, wherein said cell is a yeast cell.

26. The method of claim 25, wherein said yeast is *S. cerevisiae*.

27. The method of claim 18, wherein said cell is treated to increase its ability to take up a test compound.

28. The method of claim 18, wherein said cell has a mutation which increases its ability to take up a test compound.

29. The method of claim 28, wherein said cell is an *erg6* mutant of *S. cerevisiae*.

30. The method of claim 28, wherein said cell is an *ise1* mutant of *S. cerevisiae*.

31. The method of claim 28, wherein said cell is an *ISE2* mutant of *S. cerevisiae*.

32. The method of claim 28, wherein said cell is an *srb1* mutant of *S. cerevisiae*.

33. The method of claim 18, wherein said counterselectable reporter gene is selected from the group consisting of *URA3*, *LYS2*, *GAL1*, *CYH2*, and *CAN1*.

34. The method of claim 18, wherein said counterselectable reporter gene is operably linked to a promoter which carries an upstream repressing sequence.

35. The method of claim 34, wherein said counterselectable reporter gene is operably linked to a *SPO13* promoter.

36. The method of claim 18, wherein said DNA-binding-protein recognition site comprises at least one binding site for a protein selected from the group consisting of GAL4, LexA, and Ace1.

37. The method of claim 18, wherein the number of said DNA-binding-protein recognition sites is between 1 and 20.

38. The method of claim 18, wherein said DNA-binding moiety comprises the DNA-binding domain of a protein selected from the group consisting of GAL4, LexA, and Ace1.

39. The method of claim 18, wherein said gene activating moiety comprises the transcription activation domain of a protein selected from the group consisting of GAL4, VP16, and Ace1.

40. A method for determining whether a first test protein is capable of interacting with a second test protein and incapable of interacting with a third test protein, said method comprising:

(a) providing a cell which contains:

(i) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising said first test protein covalently bonded to a gene activating moiety;

(ii) a reporter gene operably linked to a first DNA-binding-protein recognition site;

(iii) a second fusion gene which expresses a second hybrid protein, said second hybrid protein comprising said second test protein covalently bonded to a first DNA-binding moiety which is capable of specifically binding to said first DNA-binding-protein recognition site and which is incapable of specifically binding to a second DNA-binding-protein recognition site;

(iv) a counterselectable reporter gene operably linked to said second DNA-binding-protein recognition site; and

(v) a third fusion gene which expresses a third hybrid protein, said third hybrid protein comprising said third test protein covalently bonded to a second DNA-binding-moiety which is capable of specifically binding to said second DNA-binding-protein recognition site and which is incapable of binding to said first DNA-binding-protein recognition site;

(b) maintaining said cell under conditions such that expression of said reporter gene does not inhibit growth of said cell and expression of said counterselectable reporter gene inhibits growth of said cell; and

(c) detecting growth of said cell and expression of said selectable reporter gene as a measure of the ability of said first test protein to interact with said second test protein and the inability of said first test protein to interact with said third test protein.

41. The method of claim 40, wherein the ability of said first test protein to interact with said second test protein and not with said third test protein is measured in the presence of a test compound.

42. The method of claim 40, wherein said first test protein comprises a randomly generated peptide sequence.

43. The method of claim 40, wherein said cell is a yeast cell.

44. The method of claim 43, wherein said yeast is *S. cerevisiae*.

45. The method of claim 40, wherein said counterselectable reporter gene is selected from the group consisting of *URA3*, *LYS2*, *GAL1*, *CYH2*, and *CAN1*.

46. The method of claim 40, wherein said reporter gene is selected from the group consisting of *LEU2*, *TRP1*, *HIS3*, and *LacZ*.

47. The method of claim 40, wherein said counterselectable reporter gene is operably linked to a promoter which carries an upstream repressing sequence.

48. The method of claim 40, wherein said counterselectable reporter gene is operably linked to a *SPO13* promoter.

49. The method of claim 40, wherein said DNA-binding-protein recognition site comprises at least one binding site for a protein selected from the group consisting of GAL4, LexA, and Ace1.

50. The method of claim 40, wherein the number of each of said first and second DNA-binding-protein recognition sites is between 1 and 20.

51. The method of claim 40, wherein said DNA-binding moiety comprises the DNA-binding domain of a protein selected from the group consisting of GAL4, LexA, and Ace1.

52. The method of claim 40, wherein said gene activating moiety comprises the transcription activation domain of a protein selected from the group consisting of GAL4, VP16, and Ace1.

53. A method for determining whether a first test RNA molecule is capable of interacting with a test protein, said method comprising:

(a) providing a first population of mating competent cells, wherein a plurality of the cells of said population contain:

(i) a first selectable/counterselectable reporter gene operably linked to a first DNA-binding-protein recognition site;

(ii) a first fusion gene which expresses a first hybrid RNA molecule, said RNA molecule comprising said test RNA molecule covalently bonded to a first non-random RNA molecule; and

(iii) a second fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a DNA-binding moiety which is capable of specifically binding to said DNA-binding-protein recognition site, said DNA-binding moiety being covalently bonded to an RNA-binding moiety, wherein said RNA-binding moiety is capable of specifically binding to said non-random RNA molecule;

(b) providing a second population of mating competent cells, wherein a plurality of the cells of said population contain:

(i) a second selectable/counterselectable reporter gene operably linked to a second DNA-binding-protein recognition site; and

(ii) a third fusion gene which expresses said test protein covalently bonded to a gene activating moiety; and

(c) maintaining said first and said second populations of mating competent cells, independently, under conditions such that expression of said selectable/counterselectable reporter genes inhibits growth of the cells of said populations;

(d) mixing said first and said second populations of mating competent cells under conditions conducive to formation of mated cells; and

(e) detecting expression of said selectable/counterselectable reporter genes as a measure of

the ability of said test RNA molecule to interact with said test protein.

54. The method of claim 53, wherein said test RNA molecule comprises a randomly generated RNA sequence.

55. The method of claim 53, wherein said test protein comprises a randomly generated peptide sequence.

56. The method of claim 53, wherein said ability is measured in the presence of a test compound.

57. The method of claim 53, wherein the cells of said populations of cells are yeast cells.

58. The method of claim 57, wherein said yeast is *S. cerevisiae*.

59. The method of claim 58, wherein one population of cells is of the MATa mating type and the other population of cells is of the MATα mating type.

60. The method of claim 53, wherein said first and second counterselectable reporter genes are selected from the group consisting of *URA3*, *LYS2*, and *GAL1*.

61. The method of claim 53, wherein said DNA-binding moiety comprises the DNA-binding domain of a protein selected from the group consisting of GAL4, LexA, and Ace1.

62. The method of claim 53, wherein said gene activating moiety comprises the transcription activation

domain of a protein selected from the group consisting of GAL4 and Ace1.

63. The method of claim 53, wherein said first and second DNA-binding-protein recognition sites comprise at least one binding site for a protein selected from the group consisting of GAL4, LexA, and Ace1.

64. The method of claim 53, wherein the number of each of said DNA-binding protein recognition sites is between 1 and 20.

65. The method of claim 53, wherein said counterselectable reporter gene is operably linked to a promoter which carries an upstream repressing sequence.

66. The method of claim 65, wherein said counterselectable reporter gene is operably linked to a *SPO13* promoter.

67. The method of claim 53, wherein said expression of said counterselectable reporter gene is detected as inhibition of cell growth.

68. A method for determining whether a first test RNA molecule is capable of interacting with a second test RNA molecule, said method comprising:

(a) providing a first population of mating competent cells, wherein a plurality of the cells of said population contain:

(i) a first selectable/counterselectable reporter gene operably linked to a first DNA-binding-protein recognition site;

(ii) a first fusion gene which expresses a first hybrid RNA molecule, wherein said first hybrid RNA molecule comprises said first test RNA molecule covalently bonded to a first non-random RNA molecule; and

(iii) a second fusion gene which expresses a first hybrid protein, said first hybrid protein comprising a DNA-binding moiety which is capable of specifically binding to said DNA-binding-protein recognition site, said DNA-binding moiety being covalently bonded to a first RNA-binding moiety which is capable of specifically binding to said first non-random RNA molecule;

(b) providing a second population of mating competent cells, wherein a plurality of the cells of said population contain:

(i) a second selectable/counterselectable reporter gene operably linked to a second DNA-binding-protein recognition site;

(ii) a third fusion gene which expresses a second hybrid RNA molecule wherein said second hybrid RNA molecule comprises said second test RNA molecule covalently bonded to a second non-random RNA molecule; and

(iii) a fourth fusion gene which expresses a gene activating moiety covalently bonded to a second RNA-binding moiety which is capable of specifically binding to said second non-random RNA molecule; and

(c) maintaining said first and said second populations of mating competent cells, independently, under conditions such that expression of said counterselectable reporter genes inhibits growth of said cells;

(d) mixing said first and said second populations of mating competent cells under conditions conducive to formation of mated cells; and

(e) detecting expression of said counterselectable reporter genes as a measure of the ability of said first test RNA molecule to interact with said second test RNA molecule.

69. The method of claim 68, wherein said first test RNA molecule comprises a randomly generated RNA sequence.

70. The method of claim 68, wherein said second test RNA molecule comprises a randomly generated RNA sequence.

71. The method of claim 68, wherein said ability of said first and said second RNA molecules to interact is measured in the presence of a test compound.

72. The method of claim 68, wherein the cells of said populations of cells are yeast cells.

73. The method of claim 72, wherein said yeast is *S. cerevisiae*.

74. The method of claim 73, wherein one said population of cells is of the MATa mating type and the other said population of cells is of the MATα mating type.

75. The method of claim 68, wherein said first and second counterselectable reporter genes are selected from the group consisting of *URA3*, *LYS2*, and *GAL1*.

76. The method of claim 68, wherein said DNA-binding moiety comprises the DNA-binding domain of a protein selected from the group consisting of GAL4, LexA, and Acel.

77. The method of claim 68, wherein said gene activating moiety comprises the transcription activation domain of a protein selected from the group consisting of GAL4, VP16, and Ace1.

78. The method of claim 68, wherein said first and second DNA-binding-protein recognition sites comprise at least one binding site for a protein selected from the group consisting of GAL4, LexA, and Ace1.

79. The method of claim 68, wherein the number of said DNA-binding-protein recognition sites is between 1 and 20.

80. The method of claim 68, wherein said counterselectable reporter gene is operably linked to a promoter which carries an upstream repressing sequence.

81. The method of claim 80, wherein said counterselectable reporter gene is operably linked to a *SPO13* promoter.

82. The method of claim 68, wherein said expression of said counterselectable reporter gene is detected as inhibition of cell growth.

83. A method for determining whether a test DNA molecule is capable of interacting with a test protein, said method comprising:

(a) providing a cell containing:

(i) a counterselectable reporter gene operably linked to said test DNA molecule;

(ii) a fusion gene which expresses said test protein covalently bonded to a gene activating moiety; and

(b) detecting expression of said counterselectable reporter gene as a measure of the ability of said test DNA molecule to interact with said test protein.

84. The method of claim 83, wherein (i) the sequence of said test DNA is randomly generated and (ii) the protein comprises a randomly generated peptide sequence.

85. A method for identifying a mutation in a reference protein which affects the ability of the reference protein to interact with a test protein, said method comprising:

(a) providing a cell containing:

(i) a counterselectable reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a selectable reporter gene operably linked to a DNA-binding-protein recognition site;

(iii) a first fusion gene expressing a first hybrid protein, said first hybrid protein comprising said test protein; and

(iv) a second fusion gene expressing a second hybrid protein, said second hybrid protein comprising said candidate mutated reference protein, wherein said candidate protein is encoded within a nucleic acid library of mutant alleles of the gene encoding said reference protein, and

wherein one of said first and said second hybrid proteins further comprises a DNA-binding moiety which is capable of specifically binding to said DNA-binding-protein recognition site, and the other of said first and said second hybrid proteins further comprises a gene activating moiety;

(b) maintaining said cell under conditions such that expression of said counterselectable reporter gene at a level equal to or greater than the level of expression obtained with said reference protein inhibits growth of said cell, and such that expression of said counterselectable reporter gene at a level less than the level of expression obtained with said reference protein does not inhibit growth of said cell; and

(c) in a separate step, maintaining said cell under conditions such that expression of said counterselectable reporter gene does not inhibit growth of said cell, and detecting expression of said selectable reporter gene as a measure of the ability of said test protein to interact with said candidate mutated reference protein.

86. The method of claim 85, further comprising comparing the sequence of said candidate mutated protein with the sequence of said reference protein as an indicator of a mutation in said reference protein which affects the ability of said reference protein to interact with said first test protein.

87. The method of claim 85, wherein said second fusion gene encodes a functional C-term tag, and expression of said selectable reporter gene is measured as an indicator of the presence of said functional C-term tag.

88. The method of claim 87, wherein said functional C-term tag comprises a binding site for pRb.

89. A method for identifying a conditional mutant of a reference protein with decreased ability to interact with a second protein under a first set of conditions and

which is capable of interacting with said second protein under a second set of conditions, said method comprising:

(a) providing a cell containing:

(i) a counterselectable reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a selectable reporter gene operably linked to a DNA-binding-protein recognition site;

(iii) a first fusion gene expressing a first hybrid protein, said first hybrid protein comprising a candidate mutated reference protein, wherein said candidate protein is encoded within a nucleic acid library of mutant alleles of the gene encoding said reference protein; and

(iv) a second fusion gene expressing a second hybrid protein, said second hybrid protein comprising said second protein, wherein:

one of said first or said second hybrid proteins comprises a DNA-binding moiety which is capable of specifically binding to said DNA-binding-protein recognition site, and

the other of said first or said second hybrid proteins comprises a gene activating moiety;

(b) maintaining said cell under conditions in which expression of said counterselectable reporter gene at a level equal to or greater than the level of expression obtained with said reference protein inhibits growth of said cell, and such that expression of said counterselectable reporter gene at a level less than the level of expression obtained with said reference protein does not inhibit growth of said cell;

(c) in a separate step, maintaining said cell under conditions such that expression of said counterselectable reporter gene does not inhibit growth of said cell, and detecting expression of said selectable reporter gene as a

measure of the ability of said candidate mutant protein to interact with said second protein; and

(d) in a separate step, maintaining the cells under conditions identical to those in step (c) except for one parameter, and detecting expression of said selectable reporter gene as a measure of the ability of said candidate mutant protein to interact with said second protein, said expression of said selectable reporter gene under step (c) conditions but not under step (d) conditions being indicative of said conditional mutant.

90. The method of claim 89, further comprising comparing the sequence of said candidate mutant protein with the sequence of said reference protein as a means for identifying a mutant of said reference protein which has a decreased ability to interact with said second protein under a first set of conditions and which is capable of interacting with said second protein under a second set of conditions.

91. The method of claim 89, wherein said parameter is selected from the group consisting of (i) temperature and (ii) presence of a drug.

92. A method for identifying compensatory mutations in a first and a second reference protein which allow a first and a second mutant reference protein to interact with each other but not with said second and said first reference proteins, respectively, said method comprising:

(a) providing a first population of mating competent cells, wherein a plurality of the cells of said population contain:

(i) a first counterselectable reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a first selectable reporter gene operably linked to a DNA-binding-protein recognition site;

(iii) a first fusion gene which expresses a first hybrid protein, said first hybrid protein comprising said first candidate mutant protein covalently bonded to a gene activating moiety, wherein said first candidate mutant protein is encoded within a nucleic acid library of mutant alleles of said first reference protein; and

(iv) a plasmid containing a first counterselectable marker, and a second fusion gene which expresses a second hybrid protein, said hybrid protein comprising said second reference protein covalently bonded to a DNA-binding moiety;

(b) providing a second population of mating competent cells, wherein a plurality of the cells of said population contain:

(i) a second counterselectable reporter gene operably linked to a DNA-binding-protein recognition site;

(ii) a second selectable reporter gene operably linked to a DNA-binding-protein recognition site;

(iii) a third fusion gene which expresses a third hybrid protein, said third hybrid protein comprising said second candidate mutant reference protein covalently bonded to a DNA-binding moiety, wherein said second test protein is encoded within a nucleic acid library of mutant alleles of said second reference protein; and

(iv) a plasmid containing a second counterselectable marker, and a fourth fusion gene which expresses a fourth hybrid protein, said hybrid protein comprising said first reference protein covalently bonded to a gene activating moiety;

(c) maintaining said first and said second populations of mating competent cells, independently, under

conditions such that expression of said counterselectable reporter genes at a level equal to or greater than the level of expression obtained with said first and second reference proteins inhibits growth of said cells;

(d) maintaining said first and said second populations of mating competent cells under conditions such that expression of said counterselectable marker inhibits growth of said cells;

(e) maintaining said first and said second populations of mating competent cells under conditions conducive to formation of mated cells;

(f) detecting expression of said selectable reporter genes as a measure of the ability of said first and said second candidate mutant proteins to interact with each other and not with said second and said first reference proteins.

93. The method of claim 92, further comprising comparing the sequences of said first and said second candidate mutant proteins which interact with each other with the sequences of said first and said second reference proteins as a means for identifying compensatory mutations in said first and said second reference proteins.

94. A yeast cell having integrated into its genome a counterselectable reporter gene which is operably linked to a promoter which comprises (i) an upstream repressing sequence and (ii) a DNA-binding-protein recognition site, wherein said yeast cell lacks

(i) a naturally-occurring protein which is substantially identical to the protein encoded by said counterselectable reporter gene, and

(ii) at least one naturally-occurring protein which, when it is expressed, confers a growth advantage on a cell containing it.

95. The yeast cell of claim 94, wherein said counterselectable reporter gene is selected from the group consisting of *URA3*, *LYS2*, *GAL1*, *CYH2*, and *CAN1*.

96. The yeast cell of claim 94, wherein said promoter is a *SPO13* promoter, and said promoter comprises at least one DNA-binding-protein-recognition site for a protein selected from the group consisting of GAL4, LexA, and Ace1.

97. The yeast cell of claim 96, wherein said cell is MaV103.

98. The yeast cell of claim 96, wherein said cell is MaV203.

99. The yeast cell of claim 96, wherein said cell is MaV99.

100. A genetic construct comprising: (*i*) a yeast origin of replication; (*ii*) a selectable marker; (*iii*) a yeast promoter; (*iv*) a nuclear localization coding signal sequence; and (*v*) a bacterial origin of replication.

101. The genetic construct of claim 100, wherein said construct is p2.5.

102. A genetic construct comprising: (*i*) a yeast origin of replication; (*ii*) a selectable marker; (*iii*) a promoter; (*iv*) a bacterial origin of replication; (*v*) a

counterselectable marker; and (*vi*) a sequence which expresses a DNA-binding moiety.

103. The genetic construct of claim 102, wherein said construct is p97.CYH2.

104. A genetic construct comprising: (*i*) a yeast origin of replication; (*ii*) a selectable marker; (*iii*) a promoter; (*iv*) a bacterial origin of replication; (*v*) a counterselectable marker; and (*vi*) a sequence which expresses a gene activating moiety.

105. The genetic construct of claim 104, wherein said genetic construct is pMV257.

106. A genetic construct comprising a counterselectable reporter gene operably-linked to a promoter, wherein said promoter comprises (i) an upstream repressing sequence and (ii) a DNA-binding-protein recognition site.

107. The genetic construct of claim 106, wherein said genetic construct is *SPAL:URA3*.